

Valerian Root: Herbal Valium?

Anxiety is a common cause of psychological distress among companion animals. For example, between twenty and forty percent of dogs referred to animal behavior clinics in North America receive a diagnosis of separation anxiety.¹ Cats suffer separation anxiety in a manner similar to dogs.²



Whether the anxiety results from separation, panic, noise phobia, or a generalized anxiety state, its behavioral expression can entail excessive vocalization, inappropriate elimination, and self-inflicted trauma. High levels of anxiety can cause cardiovascular changes and psychomotor alterations.³

Acute or extreme anxiety states often require intervention and possibly medication. Benzodiazepines (BZDs) are the most commonly prescribed treatment for generalized anxiety disorder in humans.⁴ BZDs treat generalized anxiety disorder in small animals as well, along with panic disorder, fears, and phobias.⁵ BZDs allosterically modulate GABA (gamma amino butyric acid) receptors by binding to a specific site on the GABA_A receptor, called the benzodiazepine receptor. The benzodiazepine receptor in turn increases the action of GABA, an inhibitory neurotransmitter, which reduces the likelihood of neuronal firing in the brain as a consequence of hyperpolarization following chloride ion influx.

Diazepam (DZP, Valium) is a BZD in common usage. It produces sedation, muscle relaxation, and increased appetite.⁶ Paradoxical excitation from DZP can occur in dogs. Behavioral disinhibition from DZP is observed as hostility, aggressiveness, rage reactions, irritability, and loss of behavioral control. Amnesia caused by BZDs can cause animals to “forget” learned behaviors and have difficulty learning new material, such as desensitization protocols. Diazepam-induced hepatic necrosis in cats is a rare but often fatal condition arising from oral ingestion DZP, possibly resulting from an aberrant metabolite in susceptible individuals as DZP undergoes its complex metabolism. Prenatal exposure to diazepam in cats reduces the density of BZD receptors in the brain, leading to chronic anxiety, hyperactivity, aggressiveness, fear, and learning

¹ Flannigan G and Dodman NH. Risk factors and behaviors associated with separation anxiety in dogs. *JAVMA*. 2001;219:460-466.

² Schwartz S. Separation anxiety syndrome in dogs and cats. *JAVMA*. 2003;222:1526-1532.

³ Paladini AC et al. Flavonoids and the central nervous system: from forgotten factors to potent anxiolytic compounds. *J Pharm Pharmacol*. 1999;51:519-526.

⁴ Andreatini R et al. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. *Phytotherapy Research*. 2002;16:650-654.

⁵ Simpson BS and Papich MG. Pharmacologic management in veterinary behavioral medicine. *Vet Clin Small Anim*. 2003;33:365-404.

⁶ Simpson BS and Papich MG. Op. cit.

deficits in the adult.⁷ Chronic BZD ingestion can lead to tolerance, dependence, long-term memory impairment, and altered sleep structure. Chronic use of BZDs results in fewer GABA-A receptors in the brain.⁸ Tolerance to the sedation, ataxic effects, and muscle relaxation develops after several days of treatment; until then, caregivers of geriatric patients may require additional vigilance in order to help them avoid falls. Dependence may begin to appear after just one week of BZD administration. Abrupt BZD discontinuation produces abstinence syndromes, exhibited by tremors, nervousness, and tonic-clonic seizures. The likelihood of precipitating withdrawal increases with longer treatment and higher dosages. The potential for BZD abuse necessitates client screening and careful scrutiny of refill requests.

Considering the risk profile of BZDs and particularly DZP, over-the-counter anxiolytic herbal preparations conceivably offer an attractive and natural alternative to pharmaceutical approaches. Veterinarians are at some point likely to treat patients who have been chronically ingesting sufficient quantities of herbal compounds to cause unforeseen interactions with anesthetic medications or other sedatives. Therefore, it is important for veterinarians to become familiar with readily available herbal veterinary products and to ask clients about their use of them in a non-judgmental manner, in order to avoid unanticipated drug-herb interactions that could jeopardize their patients' health. In addition, clients who would prefer a more "natural" form of anxiolysis for their animal companion will appreciate an honest and informed discussion of the safety and efficacy of herbal products.

The majority of "herbal tranquilizers" and sedatives contain the herb valerian.⁹ Valerian-impregnated chewsticks and valerian-containing treats and tablets are widely available at pet product superstores and over the Internet. Treatment with valerian, from the underground parts of *Valeriana officinalis*, dates back to ancient Greece and Rome. Soldiers in World War I used it to manage shell-shock. Many of the active constituents of valerian likely participate synergistically in the clinical response.¹⁰ However, the valepotriates and sesquiterpene constituents of the volatile oils in valerian appear to be largely responsible for its CNS effects.¹¹ Valerian gives off an odor that can be highly offensive to some humans (smelling like a locker full of old, sweaty gym socks), but cats can be strongly attracted to the aroma. In fact, in the 18th century, it was suggested that

⁷ Livezey GT, et al. Enduring effects of prenatal diazepam on the behavior, EEG, and brain receptors of the adult cat progeny. *NeuroToxicology*. 1986;7:319-334.

⁸ Poyares DR et al. Can valerian improve the sleep of insomniacs after benzodiazepine withdrawal? *Progress in Neuro-psychopharmacology & Biological Psychiatry*. 2002;26:539-545.

⁹ Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol*. 1999;51:505-512.

¹⁰ Hadley S and Petry J. Valerian. *American Family Physician*. 2003;67:1755-1759.

¹¹ Fugh-Berman A and Cott JM. Dietary supplements and natural products as psychotherapeutic agents. *Psychosomatic Medicine*. 1999;61:712-728.

cats could serve to indicate the quality of valerian in apothecaries by the strength of their attraction and reaction to it.¹²

As an anxiolytic, valerian decreases subjective feelings of somatic arousal; objective reductions in systolic blood pressure responsiveness, heart rate, and self-reported stress in humans also occur. As a sedative/hypnotic agent, valerian reduces sleep latency, improves sleep quality, and displays comparable efficacy to oxazepam for insomnia.¹³ Valerian is spasmolytic, vasodilatory, anti-arrhythmic, and antidepressant. It can help to prevent development of the withdrawal syndrome from abrupt diazepam cessation. Valerian displays affinity for GABA_A receptors and modulates GABA neurotransmission. It inhibits GABA reuptake, is a serotonin 5-HT_A agonist, inhibits monoamine oxidase uptake, and has activity at adenosine receptors.¹⁴

Valerian requires repeated dosing for optimal effectiveness, but the exact parameters for nonhuman dosages remain to be determined. Herbal sedatives such as valerian may potentiate the effects of anesthetics, barbiturates, opioids, and other CNS depressants. However, overdosage with valerian appears to be difficult, in that an intentional attempt at overdosage and suicide with 20 grams of valerian failed to produce a significant change in vital signs.¹⁵

There are no specific contraindications to valerian, although some sources advise against giving the herb to pregnant or nursing individuals. One study reported retarded ossification of rat fetuses when administered early in gestation, but no postnatal developmental changes.¹⁶ Dependency and withdrawal from chronic administration has occurred, as noted in one case report of withdrawal following sudden cessation of long-term, high dose valerian therapy mimicking withdrawal symptoms from BZDs, and reversed with BZD administration.¹⁷ Adverse effects are rare and usually minor, such as headache and morning grogginess. Cytotoxicity and mutagenicity, of unknown significance, have been reported for valepotriates; this has raised concern about long-term administration.

General concerns about safety and efficacy plague most herbal products. Because herbs can be marketed as dietary supplements, in accordance with the

¹² Foster S. Valerian. Obtained at <http://herbalgram.com/?c=valerian> on 08-30-03 .

¹³ Ziegler G et al. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non-organic insomnia – a randomized, double-blind, comparative clinical study. *Eur J Med Res.* 2002;7:480-486.

¹⁴ Yager J et al. Use of alternative remedies by psychiatric patients: illustrative vignettes and a discussion of the issues. *Am J Psychiatry.* 1999;156:1432-1438.

¹⁵ Willey LB et al. Valerian overdose: a case report. *Vet Human Toxicol.* 1995;37:364-365.

¹⁶ Tufik S et al. Effects of a prolonged administration of valepotriates in rats on the mothers and their offspring. *J Ethnopharmacol.* 1994; 41:39-44. Cited in Plushner SL. Valerian: *Valeriana officinalis.* *Am J Health-Syst Pharm.* 2000;57:328-335.

¹⁷ Garges HP. Cardiac complications and delirium associated with valerian root withdrawal [Letter]. *JAMA.* 1998;280:1566-1567.

1994 Dietary Supplement Health and Education Act, they are not subject to regulatory control, other than requirements about labeling. Content and purity may vary between batches and manufacturers. Growing conditions, preparation (tablet, dried herb, extract), and age of the product may cause products to differ in effectiveness. Adulteration of herbal products such as valerian, St. John's wort, passionflower, and echinacea with organopesticides, cadmium, and other heavy metals presents insidious dangers to patients.¹⁸ Careful examination of dietary and herbal supplements has led to the discovery of many contamination-related adulterants, including insects, microbes, undesirable plant and animal matter, and pharmaceuticals (corticosteroids, antihistamines, diuretics, antiepileptics, etc.).¹⁹ Providing information about the potential dangers, as well as the value of herbal products, allows clients to make truly informed decisions on behalf of their animal's health care.

¹⁸ Huggett DB, et al. Organochlorine pesticides and metals in select botanical dietary supplements. *Bull Environ Contam Toxicol*. 2001;66:150-155.

¹⁹ Cole MR and Fetrow CW. Adulteration of dietary supplements. *Am J Health-Syst Pharm*. 2003;60:1576-1580.